Cetrotide

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IAIN/0072	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	30/08/2019		Annex II and PL	
II/0068	Update of section 4.2 of the SmPC to specify that the starting date of treatment is depending on the ovarian response and may be delayed in absence of follicular growth, based on a literature review. The Package Leaflet (PL) is updated in accordance. In addition the	29/05/2019	01/07/2019	SmPC, Annex II, Labelling and PL	Section 4.2 of the Cetrotide SmPC has been amended to include some further information regarding ovarian response. The starting day of Cetrotide is depending on the ovarian response, i.e. the number and size of growing follicles and/or the amount of circulating oestradiol. The start

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	Marketing authorisation holder (MAH) took the opportunity to correct the timing of ovulation induction in section 3 of the PL, to delete the list of local representatives in the Package Leaflet. Furthermore, the Product Information is brought in line with the latest QRD template version 10.0. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				of Cetrotide may be delayed in absence of follicular growth, although clinical experience is based on starting Cetrotide on day 5 or day 6 of stimulation.
IB/0069	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	13/09/2018	n/a		
IA/0070	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	10/09/2018	n/a		
T/0067	Transfer of Marketing Authorisation	12/07/2018	02/08/2018	SmPC, Labelling and PL	
IB/0066	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/07/2018	01/07/2019	PL	
II/0064	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of	08/03/2018	n/a		

	change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IB/0065	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	13/12/2017	16/03/2018	SmPC, Labelling and PL	
IB/0063	B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data	19/10/2017	n/a		
IB/0062	B.II.b.5.f - Change to in-process tests or limits applied during the manufacture of the finished product - Addition or replacement of an in-process test as a result of a safety or quality issue	16/10/2017	n/a		
II/0061	B.II.b.4.d - Change in the batch size (including batch size ranges) of the finished product - The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	12/10/2017	n/a		
IB/0060/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/07/2017	16/03/2018	SmPC, Annex II, Labelling and PL	
IA/0059	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or	16/05/2017	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
II/0058	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes	21/04/2017	n/a		
II/0056	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	06/04/2017	16/03/2018	SmPC	
IB/0057	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	04/04/2017	n/a		
PSUSA/633/201604	Periodic Safety Update EU Single assessment - cetrorelix	01/12/2016	n/a		PRAC Recommendation - maintenance
II/0052/G	This was an application for a group of variations. Update of section 4.3 in order to delete contraindications in postmenopausal women and patients with moderate renal impairment and hepatic impairment and section 4.4 to add additional warnings regarding hepatic and renal impairment. Furthermore, sections 4.4 and 4.8 have been updated regarding allergic reactions, section 4.4 regarding congenital	28/04/2016	20/04/2017	SmPC, Labelling and PL	Cases of allergic/pseudoallergic reactions, including life-threatening anaphylaxis with the first dose have been reported. The prevalence of congenital anomalies after the use of assisted reproductive technologies (ART) with or without GnRH antagonists may be slightly higher than after spontaneous conceptions although it is unclear whether this is related to factors inherent to the couple's infertility or the ART procedures. Limited data from clinical follow-up studies

	anomalies and section 4.5 to reflect the new safety data. All proposed changes to the SmPC are in line with the updated company Core Safety Data Sheet (CSDS). The Package Leaflet is updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to bring Annex IIIA in line with the latest QRD template version 10 and to update the contact details of the local representatives in Malta and Spain in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				in 316 newborns of women administered cetrorelix for infertility treatments suggest that cetrorelix does not increase the risk of congenital anomalies in the offsprings. No formal drug-drug interaction studies have been performed with cetrorelix. However, the possibility of interactions with gonadotropins or products that may induce histamine release in susceptible individuals cannot be totally excluded. Cetrorelix has not been studied in patients with hepatic impairment and caution is therefore warranted. Cetrorelix has not been studied in patients with renal impairment and caution is therefore warranted. Cetrorelix is contraindicated in patients with severe renal impairment. In addition, there is no contraindication against the use of cetrorelix in postmenopausal women.
IB/0051/G	This was an application for a group of variations. B.II.e.6.z - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Other variation B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	18/09/2015	n/a		

IG/0500	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	17/11/2014	n/a		
IB/0049	To delete the 3 mg presentation. In addition minor editorial inconsistencies were corrected. C.I.7.b - Deletion of - a strength	08/09/2014	28/11/2014	SmPC, Labelling and PL	
IG/0461	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	22/07/2014	n/a		
IB/0047	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/03/2014	28/11/2014	SmPC, Annex II, Labelling and PL	
IA/0046/G	This was an application for a group of variations. B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test A.7 - Administrative change - Deletion of manufacturing sites	17/01/2014	n/a		
IA/0045	A.7 - Administrative change - Deletion of manufacturing sites	13/12/2013	28/11/2014	Annex II and PL	

IAIN/0044	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	06/12/2013	28/11/2014	Annex II and PL	
N/0043	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/07/2013	28/11/2014	PL	
IG/0224	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/10/2012	n/a		
II/0040/G	This was an application for a group of variations. To delete an active substance manufacturer. To include an Active Substance Manufacturer File (ASMF) by a currently authorised active substance manufacturer who will now performed all steps of the sinthesis. The ASMF will replace all currently approved data on the active substance. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation A.7 - Administrative change - Deletion of manufacturing sites	24/05/2012	24/05/2012		
IB/0039/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	10/04/2012	n/a		

	B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)				
IB/0041	B.V.c.1.b - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - The implementation of the change requires further supportive data	14/03/2012	n/a		
II/0037	To introduce a post approval change management protocol. B.II.g.2 - Design Space - Introduction of a post approval change management protocol related to the finished product	17/11/2011	17/11/2011		
IA/0038	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	26/10/2011	n/a		
IB/0036/G	This was an application for a group of variations.	25/07/2011	n/a		

	B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/12/2010	n/a	PL	
IA/0035	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	28/10/2010	n/a		
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/03/2010	n/a	PL	
N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/10/2009	n/a	PL	
IA/0031	IA_01_Change in the name and/or address of the marketing authorisation holder	13/07/2009	n/a	SmPC, Labelling and PL	
IA/0030	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	10/06/2009	n/a		
IA/0029	IA_05_Change in the name and/or address of a manufacturer of the finished product	14/05/2009	n/a		
R/0028	Renewal of the marketing authorisation.	22/01/2009	25/03/2009	SmPC, Annex II, Labelling	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of

				and PL	this medicinal product continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Stalevo continues to be favourable. Changes to the Product Information have been implemented, in accordance with the current QRD template. The CHMP was of the opinion that the renewal could be granted with unlimited validity.
II/0026	Update of or change(s) to the pharmaceutical documentation	24/07/2008	04/08/2008		
IA/0027	IA_09_Deletion of manufacturing site	02/06/2008	n/a		
IB/0025	IB_38_c_Change in test procedure of finished product - other changes	22/01/2008	n/a		
IA/0024	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	18/01/2008	n/a	Annex II and PL	
N/0022	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/06/2007	n/a	PL	
IB/0021	IB_33_Minor change in the manufacture of the finished product	24/01/2007	n/a		
II/0020	Update to the Product Information (administrative). Update of Summary of Product Characteristics, Labelling and Package Leaflet	21/09/2006	17/10/2006	SmPC, Annex II, Labelling and PL	The scope of this variation was to bring the format of the Summary of Product Characteristics, Labelling and Package Leaflet of Cetrotide in line with the latest QRD template. In addition, section 4.8 (Undesirable effects) of the SPC has been restructured in accordance to the SPC guideline. This variation is of administrative nature, and it relates only to the

					new format of the Product Information.
IA/0019	IA_05_Change in the name and/or address of a manufacturer of the finished product	24/05/2006	n/a	Annex II and PL	
N/0018	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/05/2005	n/a	PL	
IB/0017	IB_38_c_Change in test procedure of finished product - other changes	21/09/2004	n/a		
IB/0016	IB_38_c_Change in test procedure of finished product - other changes	21/09/2004	n/a		
R/0015	Renewal of the marketing authorisation.	24/03/2004	17/08/2004	SmPC, Annex II, Labelling and PL	Based on their review of the available information, the CHMP was of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered by consensus that the benefit/risk profile of Cetrotide continues to be favourable for the treatment of Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation followed by oocyte pick-up and assisted reproductive techniques. The CHMP recommended therefore the renewal of the Marketing Authorisation for Cetrotide. The renewal required amendments to the terms of the Community Marketing Authorisation. The following annexes have been amended: I and IIIB. Based on their review of the available information, the CHMP was of the opinion that the quality, the safety and the efficacy of this medicinal product continues to be adequately

					and sufficiently demonstrated and therefore considered by consensus that the benefit/risk profile of Cetrotide continues to be favourable for the treatment of Prevention of premature ovulation in patients undergoing a controlled ovarian stimulation followed by oocyte pick-up and assisted reproductive techniques. The CHMP recommended therefore the renewal of the Marketing Authorisation for Cetrotide. The renewal required amendments to the terms of the Community Marketing Authorisation. The following annexes have been amended: I and IIIB.
I/0014	12_Minor change of manufacturing process of the active substance	17/11/2003	19/11/2003		
II/0013	Quality changes	25/09/2003	29/09/2003		
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/02/2003	06/03/2003	PL	
II/0011	Update of Summary of Product Characteristics	17/10/2002	15/01/2003	SmPC	
I/0010	03_Change in the name and/or address of the marketing authorisation holder	15/03/2002	19/04/2002	SmPC, Labelling and PL	
I/0009	01_Change in the name of a manufacturer of the medicinal product	15/03/2002	19/04/2002	Annex II and PL	
II/0007	Update of Summary of Product Characteristics and Package Leaflet	31/05/2001	20/09/2001	SmPC and PL	
II/0008	Change(s) to shelf-life or storage conditions	02/04/2001	02/05/2001		

T/0006	Transfer of Marketing Authorisation	16/01/2001	20/03/2001	SmPC, Labelling and PL	
I/0005	11_Change in or addition of manufacturer(s) of active substance	19/12/2000	20/02/2001		
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/02/2000	23/06/2000	PL	
I/0002	01_Change following modification(s) of the manufacturing authorisation(s)	23/08/1999	14/09/1999		
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/07/1999	16/09/1999	PL	